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A Narrowed Look into Plant-Derived Testosterone 5α-Reductase Inhibitors for Androgenetic Alopecia

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Abstract

Androgenetic alopecia (AGA) is the most prevalent cause of hair loss in men and women, resulting from a combination of genetic susceptibility and androgen hormones. Increased activity of testosterone 5α-reductase in hair follicles leads to increased synthesis of dihydrotestosterone (DHT). DHT's destructive effect on hair follicles is one of the leading reasons for hair loss. Conventional pharmacotherapeutic treatments, *e.g.* finasteride and minoxidil, are frequently accompanied by adverse effects and may be ineffective for certain people. Recent years have seen a rise in research on plant-derived testosterone 5α-reductase enzyme inhibitors. These herbal substances produced by various plant extracts and natural ingredients show promise in terms of fewer side effects and improved tolerability. This mini review investigates herbal testosterone 5α-reductase inhibitors for treatment AGA.

Key Words: Androgenetic alopecia, testosterone, 5α-reductase, 5α-reductase inhibitors, herbal 5α-reductase inhibitors

1. Introduction

Hair loss (alopecia) is a frequent and non-contagious condition in modern culture, affecting people of all sexes and ages. It can be caused by a variety of variables, including genetics, hormonal changes, stress, pharmaceutical usage, or side effects from any therapy. In other words, alopecia is a disorder caused by the weakening of hair follicles on the scalp or other parts of the body where hair grows for a variety of reasons. Hair loss has been a common worry for many people in many nations in recent years, mainly mostly to the pressures associated with contemporary living (Aukerman & Jafferany, 2023; Liu, Xu, Meng, Liu, & Liu, 2024). According to a statistical analysis performed at a dermatology clinic, the proportion of patients requesting treatment for hair loss headed from 1.24% in 2010 to 9.44% in 2020. The number of female patients requesting therapy for hair loss increased significantly during the previous 10 years. Furthermore, the study concluded that the prevalence of androgenetic alopecia (AGA) increased the most from 17% in 2010 to 32% in 2020. The study's clinic visits comprised 30.6% for AGA, 19.3% for alopecia areata, 15.4% for telogen effluvium, 14.9%

for seborrheic dermatitis, and 7.1% for lichen planopilaris (Lyakhovitsky *et al.*, 2023). A study of 226 patients aged 10 to 16 years old revealed that complaints of hair loss in pediatric patients doubled over 10 years. The rise was most typically observed among boys (Xiao *et al.*, 2006). According to a study (Al Najjar *et al.*, 2023), half of men and one-third of women will get alopecia over their entire lives. Hair loss is a common health issue in daily life. Typically, shedding between 25 to 125 hairs *per* day is considered typical. However, this number may vary by gender. Because there is no degeneration or lack of hair follicles, this condition is not deemed pathologic. However, shedding more than an average of 100 hairs each day might suggest pathological hair loss (Chumlea *et al.*, 2004; Katharina, Wolf-Bernhard, & Christoph, 2004; Semalty, Semalty, Joshi, & Rawat, 2011). Alopecia not only affects people's physical appearance, but also causes psychological, mental, and social problems. In other words, it may have a substantial influence on people's quality of life, mental health, and even self-esteem, as well as their social lives. Patients with alopecia have much greater rates of sadness and anxiety than others (Al Najjar *et al.*, 2023). A study conducted in Poland revealed that 60% of Polish men feel ashamed of hair loss, 81.3% experience stress in their daily lives, and 66.7% report a significant impact on their self-esteem (Adamowicz, Załęcki, Dukiel, & Nowicka, 2022). Therefore, novel and effective drugs to treat AGA and other types of hair loss are needed.

2. Method

A literature search was conducted on Scopus, Web of Science, Google Scholar Library, and PubMed to evaluate the relationship between AGA and the enzyme known as testosterone 5α-reductase. Various filters were used to search for articles in English. The following search terms were utilized: androgenetic alopecia, testosterone 5α- reductase, AGA treatment, AGA treatment methods, finasteride, herbal 5α- reductase inhibitors, and plants against alopecia.

3. Causes of Alopecia

Gender, age, and race may all affect the prevalence of alopecia. While numerous disorders can induce alopecia, several treatments can also lead to alopecia as a side effect (Al Najjar *et al.*, 2023). Hormonal changes (*i.e.* pregnancy, menopause), eating habits, obesity, autoimmune illnesses, hormonal problems, and stress could lead to alopecia. The decrease in estrogen levels after menopause also causes baldness. When alopecia develops as a result of another disease, the underlying cause should be identified. This method also helps cure disease-related alopecia. Alopecia may also result from a few autoimmune illnesses. Thyroid issues, such as hypothyroidism and hyperthyroidism, can lead to alopecia by inducing hair loss through a condition known as alopecia areata, in which the body views its own hair follicles as alien dangers. Stress can cause temporary hair loss problems, such as telogen effluvium. During times of high stress, changes in hormone levels occur in the body, which can lead to hair loss. Stress management and psychological assistance are essential for successfully treating this form of hair loss. Hair loss can also be caused by nutritional deficits, particularly those involving iron, zinc, B vitamins, or protein. Therefore, maintaining a balanced diet is vital. Alopecia can also be seen in polycystic ovary syndrome (PCOS), a common endocrine condition in women. In this condition, there is an excessive production of androgen hormones in women, which can lead to androgenetic-type hair loss.

Oxidative stress is characterized by an imbalance between normal oxidation and antioxidant defense mechanisms in cells, resulting in an increase in reactive oxygen species (ROS). ROS can cause damage to biomolecules such as DNA, proteins, and lipids within the cell. Oxidative stress is

known to play a role in many diseases, including aging, cancer, cardiovascular diseases, and neurodegenerative diseases. Hair follicles are protected against oxidative damage through antioxidant enzymes. However, in some cases, such as aging, hormonal changes or environmental factors, antioxidant defense mechanisms may be inadequate, leading to augmented oxidative stress. In this scenario, damage to hair follicles may increase, accelerating hair loss. The effect of DHT on hair follicles may also be a mechanism for oxidative stress. DHT can upsurge ROS production or weaken the antioxidant defense system in hair follicle cells. This can increase oxidative stress in hair follicles, accelerating hair loss. Additionally, the role of oxidative stress in the pathogenesis of AGA may be associated with cellular aging in hair follicles. Cellular aging involves the loss of cellular functions and even the acquisition of resistance to cell death. This can affect the normal cycle of hair follicles, leading to changes in the hair growth cycle and triggering hair loss. As a result, oxidative stress is thought to play a role in the pathogenesis of AGA and may accelerate hair loss. Antioxidants might potentially be beneficial in preventing and treating hair loss. Antioxidants can reduce oxidative damage to hair follicles, helping to keep hair healthier and prevent hair loss. Additionally, antioxidants may promote hair growth and support the renewal of hair follicles (Cwynar, Olszewska-Słonina, & Czajkowski, 2020; Prie, Iosif, Tivig, Stoian, & Giurcaneanu, 2016; Trüeb, 2009). Between October 2014 and May 2015, an in-depth analysis was undertaken at the Elias Dermatology Hospital and Dermatology Clinic in Bucharest (Romania), meticulously gathering plasma samples from 27 individuals grappling with AGA. This investigation precisely quantified levels of Trolox equivalent antioxidant capacity (TEAC), malondialdehyde (MDA), and total thiols within the plasma of each participant. Furthermore, it delved into assessing the activities of key antioxidant enzymes such as superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT) alongside TEAC activity in the erythrocyte samples. Remarkably, the conclusion of this exploration revealed a pronounced reduction in SOD activity among the AGA patients, alongside a notable decline in TEAC activity and an escalation in MDA levels within their plasma samples, signaling an upsurge in oxidative stress.

This pivotal research unequivocally verified oxidative stress's involvement within the dermal papillae of individuals afflicted by AGA (Prie *et al.*, 2016). Complementarily, a parallel investigation in Türkiye probed the linkage between oxidative stress and AGA, focusing on 33 male patients, aged 18 to 30, diagnosed with the condition. This study measured total oxidant levels (TOS), total antioxidant levels (TAS), and the oxidative stress index (OSI), uncovering significantly elevated TOS and OSI values in AGA sufferers, despite unchanged TAS levels, thereby identifying increased oxidative stress in these young individuals.

These investigations collectively underscore the critical role of oxidative stress in the etiopathogenesis of AGA, advocating for further molecular research to unravel the complexities of this condition more thoroughly (Kaya Erdogan *et al.*, 2017). Moreover, they propose the contemplation of incorporating topical or systemic antioxidants into AGA treatment protocols, highlighting a potentially pivotal approach to managing this condition.

4. Androgenetic alopecia (AGA)

AGA unfolds through a nuanced process whereby hair follicles progressively diminish in size, leading to the transformation of robust terminal hairs into delicate and vellus-like strands. This transformation triggers a reduction in the anagen phase's duration—the critical period that dictates hair length within the

cycle of hair growth—while extending the telogen phase. Such shifts not only render newly emerged hairs noticeably shorter but also contribute to the gradual miniaturization of hair follicles, paving the way for the emergence of a balding visage. As the follicles miniaturize, the hairs they produce become increasingly finer, shorter, and less vibrant in color. In certain instances, this process may also give rise to microinflammations within the follicles. Though AGA is predominantly categorized under non-scarring forms of alopecia, there exists a scholarly discourse suggesting its classification as both scarring and non-scarring, underscoring the complexity of its nature.

A distinct feature of AGA is the heightened sensitivity of hair follicles atop the head to androgens as time progresses, which leads to their gradual atrophy. This heightened sensitivity results in a marked shortening of the anagen phase and a prolongation of the telogen phase within the hair growth cycle. Consequently, the ongoing miniaturization of hair follicles manifests ultimately as baldness, illustrating a profound transformation in the landscape of scalp hair (Yorulmaz, 2016).

AGA stands as the predominant form of hair loss affecting both men and women. Its onset often traces back to adolescence, with its prevalence escalating progressively with age. Remarkably, statistics indicate that by the time individuals reach the age of 70, approximately 80% of men and 50% of women will have encountered the effects of AGA. This widespread condition underscores a significant aspect of the aging process, affecting a vast majority of the population to varying degrees (Al Najjar *et al.*, 2023). The pioneering research conducted by Hamilton on men with hypogonadism, characterized by delayed or absent sexual maturation, has shed light on the intricate relationship between hair loss and hormonal fluctuations, with a specific focus on variations in testosterone (Fig. 1) levels. This work has unveiled a compelling insight that the incidence of AGA is virtually nonexistent in men who underwent castration before reaching puberty or those suffering from hypogonadism. However, the external administration of testosterone to these individuals was found to potentially initiate AGA.

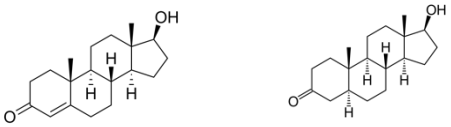

Fig. 1. Testosterone (left) and dihydrotestosterone (right)

These observations have led to the hypothesis that the genesis of AGA may be intricately linked to a complex interplay among androgens, genetic predispositions, and age-related factors, suggesting a multifaceted foundation for this common form of hair loss (Hamilton, 1951). The prevalence of AGA exhibits notable variability across different racial groups, with the highest occurrence observed in Caucasians, followed by Asians, and exhibiting the lowest incidence among Eskimos. This distinctive distribution underscores a profound genetic linkage with AGA, highlighting the influence of genetic factors on its manifestation. The patterns of hair loss associated with AGA also differ markedly between genders. In men, the condition primarily affects the temporal, frontal, and vertex (crown) regions of the scalp, leading to a receding hairline and a characteristic "horseshoe" pattern of baldness. Conversely, in women, AGA manifests through a diffuse thinning and shedding of hair, predominantly in the frontal and vertex regions, without a pronounced recession of the hairline. Hair loss in women tends to concentrate at the vertex and crown areas, and when the frontal region is more significantly impacted, the pattern of loss may resemble the shape of a "Christmas tree." This gender-specific variation in the manifestation of AGA further illustrates the complexity of the

condition and its underlying genetic and hormonal influences (Al Najjar *et al.*, 2023; Aukerman & Jafferany, 2023; Chan & Cook, 2018; Fus-Mazurkiewicz, Nowiński, Sak, Mazurkiewicz, & Król, 2024; Nestor, Ablon, Gade, Han, & Fischer, 2021).

To classify AGA, the Hamilton-Norwood scale was developed for the first time in 1951 and continues to be utilized today. This scale categorizes hair loss in men into 7 clinical stages (Norwood, 1975). Additionally, the Ludwig classification, established in 1977, grades AGA in women across three stages. This methodical approach in categorizing AGA stages has significantly contributed to the understanding and treatment of hair loss, providing a structured framework for both diagnosis and evaluation of progression in affected individuals (Ludwig, 1977). As the name suggests, the fundamental cause of AGA lies in the abundance of androgen receptors on the scalp and the hair follicles' sensitivity to androgen hormones. Particularly, DHT, a product of the reaction catalyzed by the testosterone-5α-reductase enzyme, generates a stronger androgenic signal compared to testosterone. Consequently, DHT leads to the miniaturization of hair follicles, resulting in hair thinning and loss. Consistent with this pathophysiological mechanism, individuals with AGA have elevated levels of 5-α-reductase type II, a crucial enzyme in the conversion of testosterone to DHT. In 1916, Osborn proposed that AGA could be an autosomal dominant disease, suggesting its transmission from one generation to the next (Osborn, 1916). However, Küster & Happle (1984) revisited the genetics of AGA in 1984, challenging Osborn's hypothesis by arguing that it was not sufficiently substantiated with examples, thus casting doubt on its validity. They suggested a polygenic inheritance pattern as more plausible. Studies to date support the notion that AGA possesses polygenic traits, yet its pathophysiology and genetics remain not fully understood. It has been proposed that the androgen receptor gene plays a significant role in AGA, indicating that the disorder is multifactorial, involving several genes and influenced by environmental factors as well (Ellis, Sinclair, & Harrap, 2002). There is substantial evidence and research supporting the role of androgens in the development of AGA. Even though testosterone levels in individuals with and without AGA may be similar, those with AGA tend to have higher levels of free testosterone, DHT, and active testosterone. Moreover, individuals lacking the testosterone-5α-reductase type II enzyme show a lower prevalence of AGA (Devjani, Ezemma, Kelley, Stratton, & Senna, 2023; Piraccini & Alessandrini, 2014). Yet, the pathophysiology and molecular mechanisms of AGA are still not entirely elucidated. The diagnosis of AGA is established through the patient's history and specific tests. The area of hair loss and its severity are determinative. An early diagnostic feature of AGA is an increase in fine, vellus hairs and a reduction in hair shaft diameter by approximately 20% compared to normal (De Lacharrière *et al.*, 2001; Kaliyadan, 2022; Lolli *et al.*, 2017). Various scales are used to assess the severity of hair loss. The "Norwood-Savin Scale" is one of the most commonly used for classifying hair loss in men, while the "Ludwig Scale" or "Sinclair Scale" is used for women. Diagnosis begins with a physical examination, where the hairline, hair density, pattern of hair loss, and other signs on the scalp are evaluated. This helps identify the typical signs of androgenic alopecia, such as a receding hairline and thinning hair at the crown. Examination with a dermatoscope can reveal characteristic findings of AGA, including thinning of hair follicles, miniaturization of the hair, and changes in scalp pigmentation. Laboratory tests to assess androgen levels, particularly free and total testosterone and dehydroepiandrosterone sulfate (DHEAS), can also assist in the diagnosis (Alves, 2017;

Devjani *et al.*, 2023; Piraccini & Alessandrini, 2014).

4.1. Treatment of AGA

Despite its widespread occurrence, while the diagnosis of AGA is often straightforward, there is no standard treatment guideline for managing the condition. Initiating treatment at the earliest possible stage is crucial. The selection of a treatment approach in AGA takes into account factors such as feasibility, effectiveness, and cost. The primary goal in treating AGA is to halt the miniaturization of hair follicles and to enhance hair density. Typically, AGA treatments aim to slow hair loss, increase hair density or promote hair regrowth.

Currently, oral finasteride and topical minoxidil are the only two American Food and Drug Administration (FDA)-approved medications for AGA treatment. In 1997, the FDA approved the use of finasteride at a daily dose of 1 mg for men with mild to moderate AGA. Nevertheless, due to its teratogenic effects, it is advised that women either do not use finasteride or use it in conjunction with suitable contraception methods. Numerous clinical studies and meta-analyses have validated the effectiveness of oral finasteride in AGA treatment.

Minoxidil is available as a 2% solution (primarily for women) and a 5% solution or foam (primarily for men) with the recommended dosage being 1 ml applied once or twice daily. The foam formulation, which does not contain propylene glycol, tends to irritate the scalp less. Initially used as an antihypertensive medication, minoxidil was observed to cause hypertrichosis as a side effect, which led to its application in AGA treatment. In the scalp, the sulfotransferase enzyme converts minoxidil to its active metabolite, minoxidil sulfate. Although the exact mechanism of action of minoxidil remains partially understood, several hypotheses exist.

Besides these FDA-approved treatments, numerous other therapeutic methods without FDA approval are currently employed in AGA management. Treatment is not limited to pharmacotherapy but also includes various physical and complementary therapeutic approaches (Alzaid, 2023; Devjani *et al.*, 2023; Ellis *et al.*, 2002; Feldman *et al.*, 2023; Fus-Mazurkiewicz *et al.*, 2024; Liu *et al.*, 2024; Lolli *et al.*, 2017). In recent years, the FDA has approved the combined treatment method of topical minoxidil and oral finasteride for AGA management (Trilisnawati *et al.*, 2021). The effects of finasteride and minoxidil treatment begin to manifest after 6 months of use. Continuous lifelong treatment is necessary, as cessation of the medication results in the resumption of hair loss.

Herbal extracts and pure substances are likewise employed in the treatment of AGA. For instance, pure substances like beta-sitosterol and biochanin A (Fig. 2), as well as extracts from *Serenoa repens* (W.Bartram) Small, *Panax ginseng* C.A.Mey., *Curcuma aeruginosa* Roxb., *Cucurbita pepo* L., and *Trifolium pratense* L., have exhibited positive effects by inhibiting DHT formation.

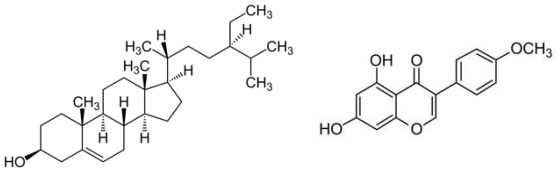

Fig. 2. Beta-sitosterol (left) and biochanin A (right)

Rosemary (*Rosmarinus officinalis* L.) extract reduces hair loss by enhancing perifollicular vascularization, while *Camellia sinensis* L. extract displayed anti-apoptotic activity, thereby reducing hair loss (Feldman *et al.*, 2023; Karaca & Akpolat, 2019; Nestor *et al.*, 2021; Ntshingila, Oputu, Arowolo, & Khumalo, 2023; Trilisnawati *et al.*, 2021). *Nigella sativa* L. seeds and the fixed oil of the seeds possess antioxidant and anti-

inflammatory activities. Thymoquinone, constituting 30-48% of its content, displayed a notable anti-inflammatory activity by suppressing pro-inflammatory cytokines like tumor necrosis factor-α (TNF-α), interleukins (IL)-3, 4, and 5. In a randomized, double-blind, placebo-controlled study conducted on 10 patients with telogen effluvium type alopecia, oil derived from *N. sativa* was applied topically daily for 3 months. The study concluded that within 3 months, there was a significant intensification in hair density and hair shaft thickness, and many patients experienced a reduction in inflammation at the hair roots (Rossi *et al.*, 2016).

Procapil™ is a complex that contains biotinoyl tripeptide-1, apigenin, and oleanolic acid ((Fig. 3). Its effects on nourishing hair follicles, preventing hair loss, and stimulating new hair growth have been proven in clinical studies. Unlike FDA-approved minoxidil and finasteride, Procapil™ does not have any reported side effects. Apigenin, a flavonoid found in Procapil™, promotes vasodilation in the capillaries of hair follicles, thereby enhancing blood flow and nutrition to the hair roots (Guerrero & Ch, 2011).

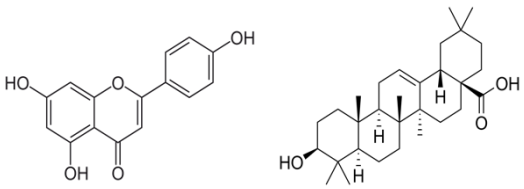

Fig. 3. Apigenin (left) and oleanolic acid (right)

However, detailed and definitive studies on the sole effect of apigenin on hair growth are still lacking. Oleanolic acid in the formulation inhibits types I and II of 5α-reductase, preventing the formation of DHT. Biotinoyl tripeptide-1 has antioxidant activity and prevents the aging of hair roots, thereby inducing the growth of new hairs (Karaca & Akpolat, 2019).

Developed by a Swiss company, Redensyl™ is a compound used to promote hair growth. It consists of various components such as dihydroquercetin glucoside, epigallocatechin gallate glucoside, glycine, and zinc. Dihydroquercetin glucoside and epigallocatechin gallate EGCG) glucoside in its content stimulated hair follicle cells and dermal papilla, inducing hair growth. Glycine is an amino acid found specifically in the proteins of the hair structure, playing a crucial role in hair metabolism (Jenkins & Powell, 1994). Zinc helps strengthen the hair structure and facilitates the binding of cysteine to keratin in the hair (Hsu & Anthony, 1971). Redensyl™ is used to prevent hair loss and promote the growth of new hair follicles.

Capixyl™, developed by a French company, is an innovative blend of red clover extract (*Trifolium pratense* L.) and biomimetic peptides. It has recently become quite popular for helping prevent hair loss (Loing, Lachance, Ollier, & Hocquaux, 2013). In a study conducted in Türkiye, Capixyl™, Procapil, and Redensyl™ were combined and evaluated against minoxidil (5%) in 120 male patients diagnosed with AGA. The combination of Capixyl™, Procapil™, and Redensyl™ exhibited considerably high success compared to that of minoxidil. While 64.7% of patients treated with the Capixyl™, Procapil™, and Redensyl™ mixture reported a significant or moderate improvement, only 25.5% of patients treated with minoxidil (5%) observed a significant or moderate improvement (Karaca & Akpolat, 2019).

In the treatment of AGA, a diverse array of therapeutic options is available, targeting various aspects of the condition's pathophysiology. These treatments range from pharmacological interventions to procedural approaches, aiming to slow hair loss, stimulate hair growth or improve hair density. Table 1 shows the mechanism of action and side effects of the methods and active substances used in the treatment of AGA.

4.2. Relationship between AGA and testosterone-5α-reductase enzyme

Testosterone, the primary male sex hormone responsible for the development of male sexual characteristics, is produced and released by the testes, ovaries, and adrenal glands in the human body. Although present in both sexes, testosterone levels are significantly higher in males. The hormone's production is regulated by the luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which are secreted by the pituitary gland located in the lower part of the brain. Testosterone plays a crucial role in numerous bodily functions, including sexual maturation and reproduction, increasing muscle mass, maintaining bone health, and metabolizing fats.

DHT, a hormone synthesized in the cytoplasm through the catalysis of testosterone by the 5α-reductase enzyme, plays a vital role in various physiological processes in males, such as sexual development and hair formation. While androgens facilitate the development of hair follicles in areas like the beard, underarms, and groin, they paradoxically inhibit hair follicle development on the scalp, leading to hair loss. Excessive amounts of DHT can contribute to health issues such as hair loss and prostate enlargement. The link between hair loss and testosterone is primarily explained through DHT, which binds to androgenic receptors in hair follicles, leading to follicle miniaturization and subsequent hair loss. In AGA, a genetic predisposition increases the sensitivity of hair follicles' androgenic receptors to DHT, thereby causing hair loss.

The enzyme testosterone-5α-reductase, which catalyzes DHT formation, exists in two isoforms, both embedded within the membrane and facilitating the conversion of testosterone to dihydrotestosterone. These enzymes, encoded by different genes, are known as testosterone-5α-reductase type I and type II. While type I exhibits maximum activity at pH 6.5, the type II enzyme operates optimally at pH 4.5, with nicotinamide adenine dinucleotide phosphate (NADPH) acting as a cofactor in this enzymatic reaction. Testosterone-5α-reductase, a membrane-bound enzyme, enhances its activity by reducing the double bonds of steroid substrates in an NADPH-dependent manner.

Moreover, the testosterone-5α-reductase type I is predominantly localized in androgen-independent organs such as skin, liver, brain, and sebaceous glands, whereas the type II enzyme is found in androgen-dependent organs such as the prostate, epididymis, and hair follicles. AGA treatment typically targets the inhibition of the testosterone-5α-reductase type II enzyme, given its localization in tissues relevant to AGA (Burns, Breathnach, Cox, & Griffiths, 2008; Sperling, 2008).

In a pivotal study conducted in 1994 by Dallob *et al.*, the role of the testosterone-5α-reductase type II enzyme in the pathogenesis of AGA was established, marking a significant step towards the current use of finasteride in AGA treatment approved by the FDA (Dallob *et al.*, 1994). Androgens exert various effects on human skin, including the growth of sebaceous glands and the elongation and development of hair. While androgens are not the sole influencers—thyroid hormones and glucocorticoids also play roles—it is widely acknowledged that androgens are the primary regulators of these processes (Inui, Fukuzato, Nakajima, Yoshikawa, & Itami, 2003; Madaan, Verma, Singh, & Jaggi, 2018).

Today, the active ingredients used in AGA treatment, *e.g.* finasteride and dutasteride, function by inhibiting the testosterone-5α-reductase. However, these drugs can have numerous side effects, including erectile

dysfunction, abnormal ejaculation, reduced ejaculation volume, severe myopathy, impaired muscle development, testicular pain, abnormal sexual function, and gynecomastia. Testosterone 5-α-reductase inhibitors are not only utilized in the treatment of AGA but are also applied in managing benign prostatic hyperplasia and prostate cancer and as part of hormone replacement therapy for transgender women (Alzaid, 2023; G.-S. Choi *et al.*, 2022; Dallob *et al.*, 1994).

Table 1: Mechanisms of action and side effects of the active substances used against AGA

Active Substance	**Mechanism of Action**	**Side Effects**
Minoxidil (Topical)	Induces arteriole vasodilation and stimulates cell proliferation and acts as a potassium channel opener.	Local irritation, itching, dry skin, and erythema
Latanoprost (Topical)	A prostaglandin analog that extends the anagen (growth) phase of the hair.	Irritation
Dutasteride (Oral)	Inhibits type I and II testosterone 5α-reductase enzymes, preventing the formation of DHT.	Erectile dysfunction, abnormal ejaculation, gynecomastia, and myopathy
Flutamide (Oral)	An antiandrogen that reduces the effect of testosterone.	Bloating, headache, and breast tenderness
Spironolactone (Oral)	An antiandrogen that reduces the effect of testosterone.	Postural hypotension
Finasteride (Oral)	Inhibits type II 5α-reductase enzyme, preventing the formation of DHT.	Erectile dysfunction, abnormal ejaculation, gynecomastia, myopathy, and psychological disorders
Bicalutamide (Oral)	An antiandrogen that reduces the effect of testosterone.	Bloating, headache, and breast tenderness
Botulinum Toxin Type A (Injection)	Blocks the effect of DHT on hair follicles.	Temporary sagging in the muscles near the injection site, and headache
Platelet-Rich Plasma (PRP)	Platelets in the plasma induce hair growth and repair through growth factors and cytokines.	Headache and bleeding at the application site
Low-Level Laser Therapy (LLLT)	Stimulates cellular proliferation and vasodilation through the induction of nitric oxide, promoting hair growth.	Urticaria
Microneedling	Stimulates the release of growth factors that promote angiogenesis.	Pain and discomfort

4.2. Plant-derived testosterone-5α-reductase inhibitors

Plant-derived natural compounds with testosterone 5α-reductase inhibitory effect are used to slow down hair loss in conditions like AGA or to combat situations such as prostate enlargement by blocking the conversion of testosterone to DHT. Previous studies have demonstrated that extracts from a variety of plants such as *Urtica dioica* Linn., *Caesalpinia bonducella* Fleming., *Tribulus terrestris* Linn., *Pedalium murex* Linn., *Sphaeranthus indicus* Linn., *Cuscuta reflexa* Roxb., *Citrullus colocynthis* Schrad., *Benincasa hispida* Cogn.,

Phyllanthus niruri Linn., *Echinops echinatus* Linn., *Ocimum basilicum* L., *Oryza sativa* L., *Polygonum multiflorum* Thunb., *Piper nigrum* L., *Piper cubeba* Bojer., *Carthamus tinctorius* L., *Phyllanthus emblica* L., *Rhinacanthus nasutus* (L.) Kurz., *Cornus officinalis* Siebold & Zucc., *Cinnamomum verum* J.Presl., *Panax ginseng* C.A.Mey., *Rosmarinus officinalis* L., *Thuja occidentalis* L., *Serenoa repens* (W.Bartram) Small., *Scutellaria baicalensis* Georgi., *Glycyrrhiza glabra* L., *Pueraria thomsonii* Benth., *Equisetum debile* Roxb. ex Vaucher., *Pueraria lobata* (Willd.) Ohwi., *Quercus acutissima* Carruth., and others have been shown to inhibit the testosterone-5α-reductase *in vitro*. Additionally, the extracts prepared from fungi such as *Ganoderma lucidum* (Curtis) P. Karst, *Polygonum multiflora* Thunb., *Platycladus orientalis* (L.)Franco, and *Cynomorium songaricum* Rupr. have also been shown to inhibit testosterone-5α-reductase both *in vitro* and *in vivo*. These findings suggest the potential therapeutic use of these natural compounds in the treatment of conditions like androgenetic alopecia, where the inhibition of the testosterone 5α-reductase could be promising.

Indeed, while a broad array of plant species has been investigated for their potential as herbal testosterone 5α-reductase inhibitors, more detailed and focused studies have been conducted on a few samples. These in-depth investigations are crucial for understanding the mechanisms through which these plants exert their inhibitory effects on testosterone 5α-reductase, as well as for determining their efficacy, optimal dosages, and potential side effects. A closer look at some of the species that have been subject to more detailed studies is given below:

- *Serenoa repens* (W.Bartram) Small (Saw Palmetto)

One of the most extensively studied plants in relation to testosterone 5α-reductase inhibition is saw palmetto. Research has revealed that its extract can effectively inhibit both isoforms of the testosterone 5α-reductase. Clinical trials have explored its use in treating BPH and AGA, with some studies demonstrating its ability to improve urinary symptoms and hair growth with minimal side effects.

- *Camellia sinensis* (L.) Kuntze (Green Tea)

Green tea, particularly its constituent epigallocatechin gallate (EGCG), has been researched for its antioxidant properties and its role in inhibiting the testosterone 5α-reductase enzyme. Detailed studies have focused on its potential to prevent hair loss in AGA by reducing DHT levels. Research also explores green tea's broader health benefits, including its anti-inflammatory and anticarcinogenic properties.

- *Urtica dioica* L. (Stinging Nettle)

Stinging nettle root extract has been the subject of several studies due to its ability to block DHT by inhibiting the testosterone 5α-reductase enzyme. Research has focused on its synergistic use with other natural inhibitors and its application in treating BPH symptoms and hair loss.

- *Cucurbita pepo* L. (Pumpkin Seed)

Pumpkin seed oil has been examined for its phytosterol content and its ability to inhibit DHT production. A few studies have specifically looked at its role in treating AGA, with results indicating improvements in hair count and hair thickness.

- *Panax ginseng* C.A.Mey

Ginseng has been studied not only for its general health benefits but also for its specific action as a testosterone 5α-reductase inhibitor. Research includes exploring its effects on promoting hair growth in AGA patients, likely due to its inhibitory action on DHT as well as its ability to stimulate hair follicle cells.

These detailed studies contribute significantly to our understanding of how natural compounds can be used to combat conditions related to DHT overproduction. However, it is important to note that while these findings are promising, more research, including large-scale and controlled clinical trials, is needed to fully establish the efficacy, safety, and clinical applications of these herbal remedies (Chaiyana *et al.*, 2017; Chittur, Parr, & Marcovici, 2011; Cho, Bae, & Kim, 2010; H.-M. Choi *et al.*, 2016; Dhanotia, Chauhan, Saraf, & Dixit, 2011; Fischer, Hipler, & Elsner, 2007; Hirata, Tokunaga, Naruto, Iinuma, & Matsuda, 2007; Karunasagara *et al.*, 2020; Koseki *et al.*, 2015; Kumar, Rungseevijitprapa, Narkkhong, Suttajit, & Chaiyasut, 2012; Lee *et al.*, 2011; Murata, Noguchi, *et al.*, 2012; Murata *et al.*, 2013; Murata, Takeshita, Samukawa, Tani, & Matsuda, 2012; Nahata & Dixit, 2014; Patel, Nag, Sharma, Chauhan, & Dixit, 2014; Upadhyay, Ghosh, & Singh, 2012; Zhang *et al.*, 2016).

In an investigation aimed at determining the inhibitory effects of *Stauntonia hexaphylla* (Thunb.) Decne. leaf ethanol extract on the enzyme testosterone 5α-reductase, researchers employed both *in vitro* and *in vivo* methodologies. The experimental models for benign prostatic hyperplasia (BPH) were established using the testosterone-treated LNCaP cell line and Sprague Dawley rats to simulate the condition in both test tubes and live subjects. Results from the study indicated that *S. hexaphylla* extract effectively diminished the levels of DHT and the expression of testosterone 5α-reductase type 2, suggesting a strong inhibitory action by the extract. Hederacoside D was identified as the principal active compound within the extract, which is presumed to be responsible for these inhibitory effects (Hong et al., 2020). *In vivo* experiments conducted with the petroleum ether extract of *Garcinia kola* Heckel seeds have determined that the extract not only inhibits the enzyme testosterone 5*α* reductase but also possesses antioxidant activity. This finding adds to the therapeutic potential of the *Garcinia kola* Heckel seeds, suggesting their dual role in enzyme inhibition and antioxidation, which could be beneficial in treating AGA (Winner, Polycarp, Ifeoma, & Chinedum, 2016). An *in vivo* study was conducted to evaluate the inhibition of the testosterone 5*α*-reductase enzyme by the ethanol extract of the tubers of the plant *Colocasia esculenta* (L.) Schott. The study involved forty-five male albino rats. By the conclusion of the study, the extract was found to possess multiple bioactive properties, including anti-inflammatory, anti-alopecic (anti-hair loss), testosterone 5*α*-reductase inhibitory, anti-androgenic, lipoxygenase inhibitory, and hypocholesterolemic activities. The major compounds identified in the extract included hexadecanoic acid methyl ester, octadecanoic acid, 9-octadecenoic acid, hexanedioic acid, bis(2-ethylhexyl)ester, and 3,5-di-t-butyl phenol. Further research is needed to pinpoint which specific compounds are responsible for these effects (Tusubira et al., 2023). The inhibitory potential of *Eclipta alba* (L.) L. on testosterone 5*α*-reductase enzyme activity was the focus of an *in vitro* study. To assess this potential, extracts of *E. alba* were prepared using both methanol and petroleum ether. The study compared the inhibitory effects of these extracts to those of finasteride, a widely recognized testosterone 5*α*-reductase inhibitor. During the extraction process, *β*-sitosterol was isolated specifically from the petroleum ether extract of *E. alba.* Enzyme inhibition assays revealed the IC_{50} values for the petroleum ether extract and *β*-sitosterol to be 150.76 ± 4.56 µg/mL and 77.09 ± 3.07 µg/mL, respectively, signifying their inhibitory efficacy. For comparison, the IC_{50} value for finasteride was notably lower at 0.246 ± 0.02 µg/mL. The results underscore the substantial inhibitory capacity of the petroleum ether extract of *E. alba*, particularly due to the prominent presence of β-sitosterol, suggesting a robust

foundation for further exploration of its anti-androgenic properties (Tusubira et al., 2023).

4. Conclusion

The present mini-review reports the relationship between androgenetic alopecia and the testosterone 5α-reductase enzyme, as well as the effectiveness of plant-derived testosterone 5α-reductase enzyme inhibitors in treating AGA. AGA is a prevalent hair loss disorder caused by the interplay of genetic predisposition and androgen hormones. The testosterone 5α-reductase contributes significantly to the pathophysiology of AGA by converting testosterone to DHT, an active androgen derivative. Traditionally, testosterone 5α-reductase enzyme inhibitors (*e.g.* finasteride and dutasteride) used to treat AGA are intended to prevent hair loss by lowering DHT production. However, several of these drugs can cause major side effects, and their long-term use may be restricted. As a result, there is increased interest in plant-derived testosterone 5α-reductase enzyme inhibitors. According to the literature, various herbal substances have the capacity to block testosterone 5α-reductase and so can be utilized to treat AGA. For example, there is strong evidence that herbal treatments like saw palmetto, green tea extract, ginseng extract, chamomile extract, and turmeric inhibit the testosterone 5α-reductase and thereby prevent hair loss. While these herbal substances show promise as alternative treatments for hair follicle preservation and hair loss prevention, additional research is needed to determine their clinical effectiveness and safety. The completion of this research may result in the development of more effective and safe AGA treatment alternatives. Furthermore, in order to maximize the efficiency of these herbal substances, combination treatments and appropriate dosages must be determined. The appraisal of the research emphasizes plant-derived testosterone 5α-reductase enzyme inhibitors as talented alternatives in the treatment of AGA. This paper scrutinizes the potential of herbal testosterone 5α-reductase enzyme inhibitors to give some idea in this area. Finally, the use of plant-derived testosterone 5α-reductase enzyme inhibitors in the therapy of AGA is encouraging.

Abbreviations

AGA: Androgenetic alopecia, **CAT**: Catalase, **DHEAS**: Dehydroepiandrosterone sulfate, **DHT**: Dihydrotestosterone, **EGCG**: Epigallocatechin gallate, **FDA**: Food and Drug Administration, **FSH**: Follicle-stimulating hormone (FSH), **GPx:** Glutathione peroxidase, **IL**: Interleukin, **LH**: Luteinizing hormone, **MDA**: Malondialdehyde, **NADPH**: Nicotinamide adenine dinucleotide phosphate, **OSI**: Oxidative stress index, **PCOS**: Polycystic ovary syndrome, **ROS**: Reactive oxygen species, **SOD**: Superoxide dismutase, **TAS**: Total antioxidant levels, **TEAC**: Trolox equivalent antioxidant capacity, **TNF-α**: Tumor necrosis factor-α, **TOS**: Total oxidant levels

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